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DATE: Nov. 1962

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DEPARTMENT OF THE ARMY
Fort Detrick
Frederick, Maryland

LABORATORY INFECTIONS WITH TYPHUS BACILLI

[Following is a translation of an article by Dr. Karl Kisskalt, Hygiene Institute of the University of Koenigsberg, in the German-language periodical Zeitschrift fuer Hygiene und Infektionskrankheiten (Journal for Hygiene and Infectious Diseases), Vol LXXX, 1915, pages 145-162.]

In studying many facts on diseases that are not transmissible to animals we are dependent on voluntary or unintentional experiments on humans. Gonococci, staphylococci and streptococci diseases, scarlet fever, measles, malaria, relapsing fever, and to a great measure smallpox, have already been successfully transmitted from the sick to the healthy. With regard to cholera, we must refer primarily to Pettenkofer, Emmerich, Oergel, Zlatogoroff (Zlatogoroff, Berliner Klin. Wochenschrift, 1909, p 1972), and others. Experiments were performed with bovine tuberculosis bacilli in the controversy on the identity of human and bovine tuberculosis. Special mention must be made of the names of the American Lazear and the Peruvian Carrion, who threw light, with the heroic sacrifice of their life, on the obscurity of the diseases of yellow fever and Peruvian verruca.

Indeed, any bacteriologist has probably performed one or the other experiment for himself on a small scale. On occasion of the inquiry discussed below, I was informed of a case of laboratory infection with paratyphus: An attendant had contracted the disease by cleaning glassware. Another laboratory case with pure culture of a strain cultivated from swine intestines has already been described (Bontemps, Deutsche med. Wochenschrift, 1912, p 2370). On the other hand, in one case fresh bouillon culture of paratyphus B, about six hours old, was sucked in the mouth while using a pipet without any consequences whatsoever. The strain had been isolated about a year before from an epidemic in Rheydt (report by Prof. Reichenbach). Mac Fadyen and two assistants fell ill with melitensis infection in Mac Fadyen's laboratory. While he died of a supervening typhus infection, the other two recovered. We still know strikingly little on typhus. It is known among specialists that laboratory infections have already occurred, but there is no compilation. Consequently, I addressed numerous colleagues with a request that they fill out a questionnaire and I have received many

replies for which I express my heartiest thanks to all for filling out the questionnaire and for having helped me with references to other cases. [See Note].

(Note:] Unfortunately, at the beginning of August I received some filled out questionnaires, without my knowing who sent them. Therefore, I beg to be excused for not having used them here. If additional cases should be known, I would be grateful for information on them. I would publish from time to time a compilation of this unusual and important material for mankind.)

The questionnaire read as follows:

1. Have you come across cases of infections with pure cultures of typhus bacilli?
2. Was it pure culture for certain, or is another infection, for example with typhus stools, possible during this time?
3. How did the infection occur?
4. Were many bacilli probably taken in?
5. How long was the incubation time?
6. What was the course of the case? Mild, severe? Cultivation of bacilli, agglutination titer?
7. Are details known on the pure culture? Originating from stools, spleen, etc.?
8. Special characteristics? Easily, difficultly agglutinable? Virulence?
9. How long before the infection was it on synthetic culture media? On what ones? Was it frequently inoculated?
10. Do you know of other cases? Who can give information on them?
11. Do you know of cases in which no infection appeared, in spite of having taken in typhus bacilli in the mouth?
12. Do you expressly desire that the case be treated anonymously?
13. Did other persons become infected in the case?

I. Cases Wherein Moment of Infection with Pure Cultures Is Known.

Case I, 1. Answer to 3: Sucking the culture into the mouth by careless use of the Gruber-Widal reaction.

4: Several drops of the pure culture. The mouth was not rinsed with a disinfectant, but only with water.

5: Incubation time, 10 to 12 days.

6: The case ran its course with high fever and severe intestinal bleeding, death in about 3 weeks. Bacilli from this patient were not cultured.

7: The culture came from a mortal case of typhus treated in the hospital and also from the blood.

8: Very easily agglutinable. High virulence. In addition to the two mortal cases adduced, several severe cases of illness were caused in the family of the first case.

9: 19 months. (Reported by Dr. Mueller, Nuernberg.)

Case I, 2. 2 and 3: In the stall of a goat injected with living typhus culture. The stall attendant looking after it had eaten his breakfast in the stall while working.

5: About 14 days.

6: Average severity.

8: Well agglutinable and virulent. (Reported by Privy Councillor Lentz.)

Case I, 3. 2 and 3: By pipetting a bouillon culture of typhus.

4: A small amount of bouillon culture.

5: 14 to 20 days.

6: Mild. Agglutination, high; exact fever no longer recallable. (Reported by Dr. B. in F.)

Case I, 4. 2 and 3: Definitely pure culture. Infection due to drawing up an agar culture of typhus in an agglutination test.

4: about 2 to 3 drops of the supernatant.

5: Exactly 14 days.

6: Severe course with chills and high fever setting in. Fever lasting 25 days; severe intestinal bleeding from the third day on. Cultures grown from blood were, at least in later generations, agglutinated with typhus serum at 1:1500, with the patient's serum at least at 1:100. After 6 weeks, complete recovery. Course from 21 May to middle July 1912.

7: The culture came from the blood of a case in Vienna.

8: Agglutination at least 1:1000; virulence not tested on animals.

9: Was cultivated on agar for several weeks. (Reported by Prof. Klemensiewicz.)

Case I, 5. 2 and 3: Definitely pure culture. Mice were soaked with typhus supernatant for the purpose of a simultaneous infection. After 24 hours, they were removed from the receptacle and killed for the purpose of determining the seat of the infection in the organism of the mouse. While the animals were being removed with pincers, they struggled violently and thus the typhus bacilli adhering to the hair drifted into the atmosphere. These bacilli were breathed in by the laboratory workers.

4: Probably not many bacilli were taken in.

5: 8 days.

6: Course, average severity; cultivation of typhus bacilli from the blood. Agglutination titer not determined.

7 to 9: Pure culture came from the urine of a typhus patient, and also directly from Endo's agar medium on which the urine of patient W. from G. had been spread. Well agglutinable; virulence quite

strong. (Reported by Dr. Messerschmidt.)

Case I, 6 (Dr. Kr. in D., around 1893). 2 and 3: Patient assumed that he could also have been infected perhaps by milk on an excursion. At that time typhus was already quite rare in D. Typhus bouillon was sucked up in pipetting and entered the mouth.

4: Immediately spit out, but certainly, in spite of this, bacteria were left behind.

5: 3 weeks.

6: Very severe, with venous thrombosis; duration 50 days.

7: The culture was isolated from the spleen with the old Koch plate method and then inoculated in bouillon. Patient became infected with this bouillon. (Reported by Prof. Wolf.)

Case I, 7. 2 and 3: Most probably a pure culture. On 10 December 1907, at noon, a trace of typhus culture sucked in while pipetting (an agar culture in 10 cc. of sodium chloride solution). On 24 December, the first symptoms.

4: It was spit out immediately and the mouth thoroughly washed out with sublimate.

5: 14 1/2 days.

6: Distinctly mild. 6 weeks of hospitalization. The blood agglutinated plainly on about New Year's Day (3 weeks after exposure to the bacilli). Bacilli detected in feces and blood.

7: Isolated about one year before, probably from feces.

8: Well agglutinable.

9: Approximately one year on agar cultures. It was frequently inoculated, since it was used for daily laboratory agglutinations. (Reported by Prof. B.)

Cases I, 8 and 9. 2 and 3: While sucking a supernatant of typhus bouillon with a pipet (for the purpose of making the Widal test) some of it reached the mouth.

4: Yes; disinfection of the mouth cavity was indeed made.

5: 14 to 17 days.

6: Of case 8, 9, III 1 and 2, one had a severe course, three mild. All together they were inoculated protectively one quarter year previously with three injections of typhus bacilli in 0.1 cc., 0.5 cc. and 1 cc. (killed at 65° C. to 70° C.). The bacilli were cultured purely in all four cases from urine or stools.

7: Originating from feces.

8: Slightly agglutinable. (Reported by Prof. Fraenken.)

Case I, 10. 2 and 3: Definitely pure culture. Infection probably due to breaking test tubes in which there were supernatants of typhus bacilli.

4: No.

5: About 3 weeks.

6: Course of average severity. Typhus bacilli were cultivated from the blood. Widal test 1:200 weakly positive.

7: Unknown.

Case I, 11. 2: Infection with typhus stools very unlikely, but, naturally, not to be excluded absolutely, because I had to work up typhus stools, during the time in question, for purposes of diagnosis -- it goes without saying, observing every biological precaution.

3: During a course, I was holding an agglutination tube on a slant over my eyes against the window. While I was shaking the tube it burst. It must have been cracked. The tube emptied its contents partly on my face. A penetration of the liquid in my mouth and nose was not felt. Probably not many bacilli taken in, for I immediately disinfected my face, washed out my mouth, etc.

5: 12 to 13 days (infection on 20 or 21 August; fell ill on 2 September).

6: Course of average severity, along with bronchopneumonia lasting 3 weeks; no intestinal bleeding. Fell acutely ill; very ill on 1 September but no fever; 2 September, very ill, 39.7° C., abdominal pains, then cecum extirpation. 3 September, 39.9° C.; then continuous fever. 5 September, detection of typical typhus bacilli in the blood.

7: Pure culture only from the blood; never cultured from stools.

8: Well agglutinable.

9: Freshly cultured from stools. From Drigalski agar, once, suitably on slant agar.

It is worth noting that in spite of the possibility stated above of a further infection the accident insurance company paid full indemnity for the accident. (Reported by Dr. B. in Berlin.)

Case I, 12. 2 and 3: Pure culture. While performing Widal's reaction, a few drops of a 24-hour old bouillon culture entered the mouth. Subsequent disinfection of the mouth cavity with sublimate, phenol and potassium permanganate without success.

4: Yes.

5: Exactly 13 days.

6: Mild. Duration of fever, one week; convalescence, relatively long time. Cultivation and agglutination were not undertaken.

7: I infected myself with Camra strain, cf. my article in this publication, Vol LIV, November 1904, p 1906. The strain came from the urine and was cultured in November 1903 and was inoculated about every two months; as far as I can remember, it was on agar.

8: Cf. the above-mentioned article. (Dr. Przibram, Prague).

Case I, 13. 2 and 3: Pure culture. Beginning of October, 1901.

I was engaged in a comparative study of typhus strains from various sources. I regularly took off specimens for titration, in order to determine the production of acid. These specimens were sucked out of the various flasks with sterile pipets. The assistant had forgotten to provide one of these pipets (5 cc.) with a cotton stopper, and since the pipets were wrapped up, I did not notice anything until I had the acid liquid in my mouth. Most of it was spit out, the mouth and throat were carefully cleaned, nothing was swallowed. All day long, I gargled and rinsed; I also took 2 g. of calomel divided into two doses.

5: Exactly 14 days.

6: Case of average severity. Pronounced bronchitis with micropurulent sputum, phlebitis in the right popliteus with severe pains spreading in the foot. Bacilli were not cultivated. Agglutination titer after 4 weeks, 1:200; after 8 weeks, 1:120; after 3 months, about 1:100; after 1 year, 1:60; after 2 years, 0.

7: The culture came from a very severe, mortal case that ran its course with the picture of a pyemia and was only cleared up in the autopsy. The culture was grown from the spleen and was cultivated for 3 weeks.

8: The strain produced very much acid and strongly fermented the typical sugars. I believe that I also remember that it was very virulent.

9: 3 weeks. Inoculated in agar every week. (Reported by Dr. Gerisvold, Bergen.)

Case I, 14. 2 and 3: Pure culture. Patient received some typhus supernatant in his mouth during an agglutination test.

4: Probably many bacilli taken in.

5: At least 14 days.

6: Severe, fatal.

7, 8, 9: Unknown. (Case of Dr. H. in K.)

Case I, 15. 2 and 3: Definitely pure culture. While a wash of a typhus culture on agar was being pipetted, the tip of the pipet was obstructed by a small particle. Quick sucking confirmed this stoppage but caused, however, a bit of the supernatant to be sucked into the mouth.

4: It was a 24-hour culture that was washed with 15 cc. of liquid. About 1 cc. of this supernatant entered the mouth, but it was immediately spit out. Then the mouth was also rinsed with permanganate solution.

5: 5 days.

6: Mild course. Fever subsided after lasting 14 days. Bacilli were not cultivated.

7: Since numerous typhus strains were being worked with simultaneously, the infecting strain could subsequently no longer be determined.

8, 9: Unknown. (Case of Dr. H. in K.)

9: Cultivated definitely for a year on laboratory culture media. (Reported by Dr. Forges.)

Case I, 16. The "Hopf Case" belongs here also, although it is not a laboratory infection, but rather an attempt at murder. Hopf gave his wife typhus bacilli in chopped meat on 31 July. Neisser has already described the case (Muenchener med. Wochenschrift, 1914, p 196) and very kindly gave me the temperature chart, which is interesting, since the temperature was taken daily morning and evening from the fifth day on after the infection. The figures are [all centigrade]: 5 August, 36.8°, 38.1°; 6, 37.5°, 38.4°; 7, 38.2°, 40.0°; 8, 39.4°, 40.4°; 9, 38.6°, 39.6° (rectal); 10, 39.4°, 40.2°; 11, 39.3°, 40.0°; 12, 40.0°, 39.7°; 13, 38.4°, 39.3°; 14, 38.6°, 38.4°; 15, 37.2°, 37.2°; 16, 36.8°, 37.0°; 17, 36.9°, 37.0°; 18, 36.8°, 36.9°; 19, 36.4°. 1 September, 38.5°, 2, 37.7°, 38.9°; 3, 37.7°, 39.3°; 4, 37.8°, 39.2°; 5, 37.6°, 37.8°; 6, 37.4°, 37.7°; 7, 36.8°, 38.7°; 8, 36.7°, 37.3°; 9, 36.7°; 10, 36.7°, 37.4°; 11, 36.5°, 37.2°. (The woman had chronic arsenic poisoning at the same time.)

8: Virulent. Guinea-pigs died after 40 hours with an intraperitoneal injection of one-fifth of a loopful and after several days with one-tenth of a loopful. Strikingly easily agglutinable.

9: Probably for a long time.

13: Three other people infected themselves or were infected either by the woman or directly by means of the culture.

Case I, 17. 2: Patient was an extremely healthy and strong young man who had always enjoyed the best of health. He definitely incurred the infection by means of the culture; any other etiology is completely excluded. There were no cases of typhus at that time in the entire district of Kassel. The patient had not been outside Marburg, nor had he received any visit.

3: Infection by sucking the peritoneal exudate of a guinea-pig infected and killed with a pure culture of typhus. In this way, a trace of the exudate entered his mouth. Immediate rinses with strong disinfectants, for hours.

4: Yes, the exudate was full of typhus bacilli.

5: 14 days.

6: Very severe, death in the relapse.

7: Came from spleen.

8: Easily agglutinable, little virulent for guinea-pigs.

9: Cultivated on agar for 3 years; inoculated every 14 days.

(Case W., reported by Prof. Bonhoff.)

Case I, 18. 2 and 3: A guinea-pig was infected intraperitoneally with a typhus strain, and liquid entered the mouth cavity while the exudate was being removed from the abdominal cavity with a pipet for purposes of making aggressin studies. The exudate consisted almost exclusively of bacilli. Cells could be seen only very

sparsely microscopically.

4: At least one loopful of the exudate entered the mouth cavity.

5: 12 days.

6: The case ran a very severe course and was complicated by an early appearing cholecystitis. Typhus bacilli were cultured from the urine. After 10 years, typhus bacilli were still detected in the urine and displayed extraordinarily high virulence for guinea-pigs. The agglutination titer never was high. Patient was often used as a "typhus bacilli donor." After 10 years, no more bacilli were detected in the urine, and simultaneously the very painful attacks of cholecystitis stopped (after two treatments in Karlsbad). At present there is still an enlargement of the spleen that is detectable only by percussion. Urotropin and other remedies had no effect at all on the bacteria.

9: An old culture on agar had been used to infect the guinea-pig. (Reported by Prof. Hake, Franzensbad.)

Case I, 19. Dr. McFadyen became infected with highly virulent exudate bacteria that had been frozen at the temperature of liquid air. As a result of certain defects that were still inherent in the technique at that time and also perhaps due to the carelessness of a newly engaged assistant it could have occurred in triturating for injections. Moreover, he was suffering from chronic laboratory melitensis infection. Fatal course. (Reported by Dr. Prausnitz, Breslau.) (Cf. also Journal of Hygiene, Vol VII, 1907, p 319.)

II. Cases Wherein Infection with Pure Culture Doubtless Occurred, but Moment of Infection was Not Known

Case II, 1. 2 and 3: Definitely pure culture. (Autopsy of rabbits that had been inoculated with typhus bacilli. Infection resulted doubtless by finger contact.)

4: Questionable.

5: About 14 days (but not accurately determined).

6: Severe course with complete unconsciousness, but no complications. Duration, 4 weeks. Fever, 40° C. Some cardiac insufficiency. Bacilli were cultivated from the blood. Agglutination, 1:80+ on the eleventh day of illness.

7: The pure culture came from the collection of the Medical Clinic. It had been obtained in earlier years from the blood of a patient.

8: Easily agglutinable. For that reason the bacilli were always used for agglutination tests. Very virulent for rabbits.

9: For several years always injected in bouillon. (Reported by Prof. Rolly.)

Case II, 2. 2 and 3: Patient became infected with the same strain that was cultured from the blood of Case 2 [sic], doubtless by finger contact.

5: At the most, 3 weeks, but it may also be much less.

6: Very mild course, lasting only 10 days. Little fever. One 5-day relapse. Bacilli cultivated from the blood. Agglutination on the eighth day of illness, 1:50+.

7 and 9: From the blood of Case 1, fresh from the blood agar plates.

Case II, 3. 2 and 3: Definitely pure culture. By cleaning infected glassware.

6: Severe.

9: Long time on agar, frequently inoculated.

Case II, 4. 2 and 3: Definitely pure culture. Infection while working with pure typhus cultures, possibly by fumes.

6: Average severity.

Case II, 5. 2 and 3: Definitely pure culture. While working with pure typhus culture supernatants with which rabbits were being made bacilli carriers. The infection, here also, may have resulted from the rabbit.

6: Mild course.

7: Well agglutinable and virulent.

9: Long time on agar, frequently inoculated. (Case 3 to 5 reported by Privy Counsellor Lentz).

Case II, 6. 2 and 3: Definitely pure culture. Infection very probably by going and coming between laboratory and room. I had frequently used the same pencils that were left in the white laboratory gown, both in my room in the Institute and in my work on the pure typhus cultures.

4: Probably few bacilli were taken in.

5: 14 days.

6: Mild. Opsonins were detected in the first week, agglutinins in the second week; titer, 1:100. Bacilli cultivated from the blood in the fourth week.

7: Derived from stools.

8: Easily agglutinable. (Dr. Seitz, Leipzig).

Case II, 7. 2 and 3: Definitely pure culture. Typhus stools excluded. Patient supposes that he became infected when the syringe slipped while he was injecting a rabbit and the liquid sprayed his gown and hands. In all probability, when this happened a small drop that he did not notice entered his mouth, because his hands were immediately disinfected.

5: 60 hours until the beginning of a general feeling of ex-

haustion. First temperature reading taken 68 hours after infection: 38.9° C. (Considering the abnormally short incubation time and the incompletely determined evidence of the infection, we find it more probable that the infection occurred earlier.)

6: Course of average severity (coma, fever for 7 weeks, no appreciable diarrhea). On the first day of illness, typhus grew from the blood in a pure culture; later, typhus bacilli in the blood, not in the urine. Agglutination titer: 1:200. Free of bacilli after nine weeks.

7: Obtained from the blood of an Institute attendant, ill with typhus, on the third day of illness.

8: Easily agglutinable. Highly virulent.

9: Several months, frequently inoculated on agar with 2% glycerin. (Reported by Privy Councillor Pfeiffer, Rostock.)

Case II, 8. A student, who was suffering from a severe mental depression due to a congenital ailment, fell ill some time after he had worked with typhus bacilli in the bacteriological course. The physician who treated him came to the conclusion that it was a case of attempted suicide. Outcome: convalescence. Patient died since then.

Case II, 9. 2 and 3: Definitely pure culture. Only pure cultures were worked with, not with stools. Moment of infection cannot be specified; it is not unlikely that an aspiration occurred while sucking up a bouillon culture.

4 and 5: Unknown.

6: First symptoms on 6 March 1903; on 8 March, fever, vertigo, faintness. On 9 March, weakness, copious liquid stools. Diagnosis made on 10 or 11 March. Course of average severity.

7: Culture came from the spleen. The case had a mortal outcome. Several other cases in the same village (Erda), also very severe.

9: The culture was on agar for exactly one year and was inoculated every 2 to 3 months, occasionally also more frequently. (Dr. Lindermeier, at that time in Giessen.)

Case II, 10 and 11. 2 and 3: Pure culture. Another infection with greater likelihood excluded. Infection while working with typhus bacilli in the Imperial Health Service in the years 1885 or 1886.

6: One severe case, the other one mild.

7: Probably derived from the spleen.

9: For a long time already on synthetic culture media (gelatin and agar); frequently inoculated. (Reported by Surgeon-General Dr. Hochstetter.)

Case II, 12 to 15. 2: Definitely pure culture; typhus stools were not worked with.

3: A. Administrator S. was frequently in the laboratory in which typhus was constantly worked with (Pfeiffer's experiment). B. Fell ill in spite of protective inoculation with the same strain. C. Prof. S., working with the same strain. D. Perhaps due to a cigar.

6: Course in A, severe? Bacilli found in stools. B, mild; bacilli found in stools. C, very severe; bacilli found in empyema. D, ambulatory, but convalescence very much disturbed due to enterop-
tosis; agglutination 1:500 or 1:1000. The cultures that were grown had exactly the same virulence as the infecting one, namely 1/50 of a loopful; therefore, they probably were identical with it.

8: Virulence, 1/50 of a loopful, which had been achieved by transfer.

9: Age unknown. Cultivation on agar with animal transfers. (Reported by Prof. Marx, Frankfurt.) (Cf. Marx, Experimentelle Diagnostik und Prophylaxe der Infektionskrankheiten (Experimental Diagnosis and Prophylaxis of Infectious Diseases), 2nd edition. Berlin: Hirschwald, p 84.)

Case II, 16. Dr. L. A., Vienna, fell ill from a laboratory infection that was caused by a typhus bacillus strain that had been cultured for many years. (Reported by Prof. Fraenitz, Graz.)

Case II, 17. 2 and 3: Since I had not been working with stools or urine during the preceding month and one-half, but rather had only been concerned with pure cultures, I believe that an infection by the latter must be assumed.

6: Course of average severity. Onset, 30 October 1913. On 2 November, bacilli found in the blood; Widal positive. Protective inoculation in the year 1908; only one injection. (Reported by Dr. Kathe, Breslau.)

III. Cases Wherein It Is Not Known Whether Infection Occurred Due to Pure Culture, Stools or Urine.

Case III, 1 and 2: The same facts as in Case I, 8 and 9, including the information on the protective inoculation; only the moment of the infection was unknown and it could also be a question of stools. (Reported by Prof. Fraenken.)

Case III, 3. Female laboratory assistant in the Research Service in Koenigsberg, March 1911. Careless working. Rather mild course. Bacilli cultivated from the stools. (Miss Gr.)

Case III, 4. The same; onset, January 1913. Severe course. Bacilli cultivated. (Miss B.) The lady worked very carelessly and, for example, she was caught in the act as she was eating breakfast while using the microscope.

Case III, 5. Dr. Sch. in P. The infection definitely occurred in the research service; how, unknown. Patient frequently left the office with disinfecting himself. Died in October 1910.

Case III, 6. Miss v. A., 1913. Infected definitely in the Research Service. Mortal course. (Reported by Prof. Roemer.)

Case III, 7. A young physician who had worked in Laboratory W. (England) fell ill in 1910, in spite of previous protective inoculation, with severe typhus with high agglutination titer, bleeding and empyema. Outcome, recovery. (Reported by Dr. Suedmersen.)

Case III, 8. In the winter of 1913-14, a female laboratory assistant in B., who was concerned both with pure cultures and with stools, fell ill with typhus. (Reported by Prof. Lingelsheim.)

Case III, 9. 2 and 3. An infection with typhus stools is not excluded, however, it is not likely. N. had worked with a typhus supernatant to make a Gruber-Widal test, and had prepared hanging drops with a pure culture. Nothing definite has been determined on the occurrence of the infection.

5: Course of average severity. First symptoms, 19 December. Definite diagnosis 26 December. Agglutination 1:200+++ and typhus bacilli in the blood on 27 December 1913. Bacilli not found in stools and urine.

8: Typical strain, easily agglutinable.

9: For about three quarters of year inoculated daily on agar (Liebig's meat extract, peptone, 3% agar). (Reported by Dr. Messerschmidt.)

Case III, 10. Pat. was concerned with pure cultures as well as with stools and urine. The infection probably resulted from crushing the cover glass of a hanging drop after which she believes that she did not disinfect herself sufficiently.

5: Approximately 3 weeks.

6: Severe course (6 June to 26 September in the hospital). Typhus bacilli not cultivated. Widal four times negative; it was found to be positive only after 5 to 6 weeks, on the day before Pat. was free of fever.

7: The culture in question was an old laboratory culture that was inoculated daily on agar. (Reported by Miss K., at that time in D.)

IV. Cases Wherein Infection Definitely Resulted from Urine or Stools

Case IV, 1. Medical candidate S. became infected while examining urine from a severe case of renal typhus and suffered an extremely severe case of typhus complicated by femoral venous thrombosis and pneumonia. It was extremely probable that some of the liquid was sucked in the mouth while pipetting the urine. (Reported by Prof. Mueller, Nuernberg.)

Case IV, 2. 2: While pipetting urine of a typhus patient, some entered the mouth.

4: Quite a number of typhus colonies grew in a pure culture on the agar plate of the urine. Very little was sucked in, and afterwards the oral cavity was washed out with disinfectants.

6: Mild course, but it was protracted a long time. Cultivation from the blood. Agglutination after 8 days at least at 1:250, microscopically positive; four months after end of the infection, negative. (Reported by Dr. Ritz, Frankfurt.)

Case IV, 3. A physician inadvertently sucked a bit of blood in his mouth while making a vein puncture of a typhus patient. 14 days later, he himself fell ill. Severe course. Bacilli of the same type as the ones from the patient were cultivated from the blood, with abnormal fermentation power.

Case IV, 4. A hospital nurse who had come in contact with the preceding case fell ill. Bacilli of the same type were cultivated from her blood. She confessed later that she had infected herself on the basis of a remark intended to be facetious that typhus drives away Coli (patient was suffering from pyelocystitis due to Coli). In spite of its being forbidden, she had used the water-closet reserved for typhus patients, she was not interrogated on details (whether the infection was with urine or stools.)

V. Cases Wherein Reception of Typhus Bacilli Did Not Cause Any Illness

Case b1. An assistant received (in 1900), while performing a Widal test, about 1 cc. of a supernatant in the mouth together with the cotton stopper, due to breakage of a capillary pipet, and he swallowed the culture and the wad of cotton, due to the force of a reflex swallowing. Immediate cleansing of the mouth with sublimate and calomel therapy for several days. (Reported by Prof. Klemensiewicz.)

Case b2. A physician received (in 1904-5) typhus bouillon in the mouth while pipetting. Immediate rinsing with hydrogen peroxide. No illness resulted. (Reported by Dr. Hilgermann.)

Case b3. In the year 1902, I made a protozoa count in Isar River water. In this connection, the Isar River water, diluted in various degrees with sterilized water, was mixed with a suspension of typhus bacilli (from a 24-hour old agar culture cultivated at 37° C). On this occasion I sucked up a small amount of the Isar River water mixed with suspension through the pipet and drew it into my mouth, because the cotton wad stopper was missing from the pipet, which I had not noticed previously. I washed out my mouth with a 1% hydro-

chloric acid solution and with alcohol, and then I chewed up several apples and spit them out again, in order to clean my teeth, etc., mechanically. No illness resulted. (Reported by Prof. Emmerich.)

Case b4. Observed at least once, perhaps even twice, that a man received typhus bacilli in the mouth while pipetting pure cultures. Immediate disinfection with strong alcohol, hydrochloric acid alcohol, etc. followed. No illness appeared. (Reported by Prof. Neisser.)

Case b5. In one case, in which typhus bacilli were taken in, no illness appeared after rinsing the mouth with sublimate solution and drinking a hydrochloric acid solution. (Reported by Privy Councillor Lentz.)

Case b6. While pipetting, a very dense sodium chloride emulsion of a 24-hour old agar culture entered the mouth. Sublimate rinse; on the following day, 2 loopfuls of killed typhus culture (1 hour at 60° C.) subcutaneously. No illness. Very strong injection reaction (1907 or 1908). Around Christmas 1910, the same occurrence. Very old Drigalski plates (6 to 10 to 14 weeks old); again no illness, only rinsing with sublimate. (Reported by Dr. Konrich).

Case b7. On occasion of a Widal reaction, which at that time (1895) was still performed with the Zeiss blood-count pipet, a considerable amount of typhus bacilli supernatant was sucked into the mouth and doubtless a large part of it was swallowed, without resulting in the slightest disturbance. Immediately after aspiration, the mouth was washed out with sublimate solution and an abundant evening meal was taken. (Reported by Prof. Heymann.)

Case b8. About 0.1 cc. of typhus bacilli supernatant was sucked into the mouth with a pipet, about 50 million living microorganisms. The culture had been made highly virulent by guinea-pig transfer. The mouth was washed out with lysol, then several times with water; swallowing was carefully avoided. No illness appeared. (Reported by Dr. Suedmersen.)

Case b9. While sectioning a typhus bacilli carrying rabbit, the contents of the ball-bladder burst during the atopsy and were received in the face and mouth. Immediately numerous typhus bacilli could be detected from the saliva on Endo's culture medium. The mouth was immediately disinfected with 60% alcohol, and definitely nothing was swallowed in the first 5 minutes after reception of the bacilli. Stools in the following weeks were always negative, likewise blood tests with Widal's method, which were made once a week. The culture was quite virulent for rabbits; about 2 loopfuls per kilogram of rabbit intravenously made the animals die of typhus sepsis. (Reported by Dr. Messerschmidt.)

Case b10. Miss D. in Koenigsberg received a few drops of a bouillon culture in her mouth while pipetting. Rinsed out with hydrogen peroxide. No illness.

SUMMARY

A. Course.

Mortal: I, 1, 14, 17, 19; III, 5, 6.
Very severe: I, 6, 18; II, 14; IV, 1.
Severe: I, 4, 8; II, 1, 3, 10, 12; III, 4, 7, 10; IV, 3.
Moderately severe: I, 2, 5, 10, 11, 13, 16; II, 4, 7, 9, 17;
IV, 4.
Mild: I, 3, 7, 9, 12, 15; II, 2, 5, 11, 13; III, 1, 2, 3;
IV, 2.
Ambulatory: II, 15.

Therefore, the cases did not progress differently from the way in which typhus usually runs. Four out of thirty-six in Groups I and II were fatal; including stool and urine infections, 6 out of 50. The lethality of typhus can be computed from the number of sickness and death cases reported in Prussia for the years 1908 to 1912 as 15.0%, 14.5%, 15.0%, 14.15%, 13.8%. It is, however, certainly lower, because relatively more fatal cases than sick cases were reported. Struempell gives it as 10%; Romberg, 8% to 10%; Schottmueller, 5 to 10%.

B. Age of the Culture in Relation to the Course of the Disease.

"Years old": I, 15 mild; I, 16 (chronic arsenic poisoning) mild or of average severity.

II, 1 (after animal transfer) severe.

"Old": I, 18 very severe; II, 3 severe; II, 5 mild.

3 years old: I, 17 (after animal transfer) fatal.

19 months old: I, 1 fatal.

1 year old: I, 7 mild; I, 12 mild; II, 9 average severity.

3 months old: I, 13 moderately severe.

Several weeks old: I, 4 severe.

Fresh: II, 2 very mild.

2nd generation: I, 6 very severe; I, 11 moderately severe.

1st generation: I, 5 average severity.

Direct with urine: IV, 1 very severe; 2 mild; 3 severe; urine or stool: IV, 4 not mortal.

No difference is seen in the course with infection by old and new cultures. Cultures that had been cultivated only a short time before frequently caused a mild illness; cultures that had been on synthetic culture media for years frequently caused a severe illness. Therefore, there is no supporting factor for the assumption that the virulence of the typhus bacillus decreases for humans due to long cultivation on synthetic culture media. The virulence of the typhus bacillus with long cultivation also does not drop more than 1/10 of the original virulence for guinea-pigs.

C. Origin of the Culture in Relation to the Course of the Disease.

From blood: I, 1, from a typhus case with a fatal outcome cultivated from a group of severe illnesses, fatal course.

From blood: I, 4 severe.

From blood: II, 1 after animal transfer (strongly virulent for rabbits), severe course.

Cultivated from the blood of the preceding case; II, 2 course very mild.

With blood (not culture): IV, 3 severe.

From the spleen of a very severe, mortal case: I, 13 moderately severe course.

From the spleen: I, 6 very severe.

From the spleen after animal transfer: I, 17 fatal.

From the spleen of a very severe, fatal case: II, 9 of average severity.

Cultivated from urine: I, 12 mild.

Direct with urine: IV, 1 very severe; IV, 2 mild.

Direct with urine or stool: IV, 4 moderately severe.

Cultivated from stools: II, 6 mild; I, 8 mild; I, 9 severe (last two uncertain).

The cases are not numerous enough to be able to state whether the strains cultivated from blood and spleen are more virulent than the ones cultivated from stools. The impression is received, however, that some strains might be more virulent than others; at least a bacillus cultivated from a case with a mortal outcome never causes a mild illness. As is well known, there certainly are epidemics with mild courses and with severe courses.

D. On the number of bacilli taken in it can, indeed, be stated that very few are sufficient to cause the disease. That is shown, for example, by Case IV, 3, in which blood was sucked out of the veins [See Note]. In case I, 11, penetration of the liquid in the mouth and nose was not felt, and face and mouth were disinfected; in spite of this, illness appeared and the case had a moderately severe course. In the rest of the cases in Group I, it is usually a question of few bacilli, since the mouth was almost always disinfected, and likewise in Group II. A relationship of the number of bacilli probably taken in to the course of the disease cannot be established. In Case b8, the reception of 50 million bacilli and subsequent disinfection of the mouth did not cause illness. One cc. of typhus bouillon contains 15 million bacilli. It should be observed, with regard to bacilli taken in with urine, that Petruschky determined 180 million in 1 cc.; Tsuzuki, 30 million; Houston, 9 million and Niepraschk, 2.5 million bacilli.

([Note:] Note made on proof-reading: Severe typhus also resulted in another case from sucking in serum of a typhus patient. Jochmann, Lehrbuch der Infektionskrankheiten (Textbook of Infectious Diseases), p 51.)

E. A connection between the special properties and the severity of the course likewise cannot be established. Almost all strains are characterized as well or easily agglutinable. Strain Camra (I, 12) is accurately described in the publication referred to. One strain

(I, 13) is characterized as strongly acid forming: moderately severe course. Another strain had an abnormal fermentation capability: it is particularly noteworthy that it retained this characteristic through two additional guinea-pig transfers. (IV, 3 and 4). This agrees with earlier observations in which it is shown that the "metatyphus bacillus" likewise does not lose its characteristic properties in the body of humans. (Mandelbaum, Muenchener med. Wochenschrift, 1908. Gruber, Archiv f. Hygiene, Vol LXXX, 1913, p 272.)

F. On the relationship of the course of the disease with its virulence for animals the following summary gives particulars:

| | | |
|--|----------|---|
| Fatal course | (I, 17) | = little virulent for guinea-pigs. |
| Very severe course | (II, 14) | = 1/50 of loopful for humans. |
| Severe course | (II, 1) | = very virulent for rabbits. |
| Severe course? | (II, 12) | = 1/50 of loopful for humans. |
| Moderately severe course | (I, 2) | = virulent. |
| Moderately severe course | (I, 13) | = very virulent. |
| Moderately severe course | (II, 7) | = highly virulent |
| Moderately severe to mild course | (I, 16) | = 1/5 of loopful: death after 40 hours; 1/10 of loopful: death after days. |
| (with chronic arsenic poisoning) | | |
| Mild course | (II, 5) | = virulent. |
| Mild course | (II, 13) | = 1/50 of loopful for humans. |
| Very mild course | (II, 2) | = very virulent for rabbits. |
| Ambulatory | (II, 15) | = 1/50 of loopful for humans. |
| No illness | (b 8) | = highly virulent for humans. |
| No illness | (b 9) | = quite virulent for rabbits; they die after 2 loopfuls per kilogram intravenously. |

It can be observed from the above that its virulence for animals is only a secondary factor for the occurrence of the disease in humans. Spectacularly, even a little virulent strain produces a mortal illness; two strongly virulent ones, no illness. One strain of very great virulence for animals caused a completely different course in four cases. It is also particularly interesting that this strain was not changed in its animal pathogenesis by transfer in humans, but rather retained its virulence of 1/50 of a loopful. It has already been mentioned above that other properties also were unchanged

by human transfer. However, one has the impression that bacilli that are sucked in directly from the animal body caused a severe illness (I, 17, 18; II, 1; quite differently II, 5?; no illness b9). G. Therefore, until now it has only emerged, concerning the cause of the different course of the disease in humans, that there probably are individual strains that are especially strongly pathogenic for humans. However, this may not be the only cause, for the same strain may produce one time a mild, then a severe illness (II, 1 and 2; II, 12-15), as, indeed, in the same epidemic there are mild and severe cases. Moreover, apart from the number of bacilli, the disposition perhaps plays a part. By disposition is to be understood any peculiarity that favors the production of the disease; therefore, not only slight resistance power against microorganisms that have penetrated in the tissues, but also facility for entering or more easy access to the intestinal wall from the intestinal tube. Thus the dog is mentioned as little disposed to metallic salts illnesses when taken orally as contrasted with injections, because the dog eliminates them by vomiting and by having diarrhea. In some epidemics that I computed, the disposition to typhus amounted to about 1/5. (Zeitschr. f. Hygiene, Vol LXXVIII, 1914, p 489.) In the preceding cases, however, it does not seem admissible to draw a conclusion from the number of infections from which illness resulted (19 in which the moment of infection is known) on the number of infections in which this was not the case (9 cases), because it was understandable that, due to the inquiry, a relatively greater number of the first mentioned ones was discovered, since they had been very well known. Therefore, the only result is that the disposition is not uniform. Case b6, in which no illness appeared after two different infections, is worth mentioning; the inoculation reaction was very strong. Nevertheless, here also I should like to assume, hesitatingly, a slight disposition.

As is well-known, typhus cases are not uniformly distributed over the entire year, but rather the autumn months are most generally affected. One may think of easier infection (water conditions, etc.) and greater disposition. Our cases occurred in the following months, in so far as data were provided: 1, beginning of January (III, 4); 2, in March (II, 9; III, 3); 1, in May (I, 4); 1, in June (III, 10); 2, in August (I, 11; 16); 3, in October (I, 13; II, 17; III, 5); 1, in November (I, 12); 2, in December (I, 7; III, 9). No illness: b6 in December. Since I am still engaged in research on these problems and I still hope to receive more material, I should like, for the present, not to draw any conclusions.

H. The incubation time amounted to:

| Case No. | Days | Course | Case No. | Days | Course |
|----------|------|------------------------|----------|------|-------------------|
| I, 15 | 5 | mild | I, 13 | 14 | moderately severe |
| 16 | 6 | moderately severe (As) | 17 | 14 | mortal |

| | | | | | |
|----|-------|----------------------|-----|-----------------|----------------------|
| 5 | 8 | moderately severe | | <u>at least</u> | |
| 1 | 10-12 | mortal | 14 | 14 | mortal |
| 18 | 12 | very severe | 7 | 14.5 | mild |
| 11 | 12-13 | moderately severe | 8,9 | 14-17 | severe or mild |
| 12 | 13 | mild | 3 | 14-20 | mild |
| 2 | 14 | moderately severe | 6 | 21 | very se- vere |
| 4 | 14 | severe | 10 | 21 | moderately severe |

There appears to be no relationship of the duration of the incubation time to the course of the disease.

One case (I, 11) began so acutely that a cecum operation was performed.

I. Of the 50 persons afflicted with the disease, 7 had previously had a protective injection. In I, 8, 9 and II, 37, 38, three injections, respectively, of 0.1 cc., 0.5 cc., 1.0 cc. of a culture killed at 65° C. to 70° C. were administered one quarter of a year before; in II, 17, only one injection had been given five years before. Case II, 16 had even been injected with the same strain; in Case III, 7, the injection had to be made with Wright's method. One of the nine that did not fall ill had been inoculated protectively. This result is very unfavorable to judging the value of the protective injection. However, it must be remarked that according to present standards it had been undertaken improperly (only once or with cultures that were heated too high).

K. Naturally, it cannot be established that other measures taken after the infection may have been successful in the cases under b, since in Groups I to IV illness did appear, in spite of entirely similar steps. However, everything possible will be tried. Spitting out, rinsing out the mouth with disinfectants, avoiding swallowing in the first few minutes, are to be recommended principally. It appears to be very expedient to chew apples (b3), especially according to the experiments by Hallwachs (Zeitschr. f. Hygiene, Vol LXVII, 1910, p 373) who was able to prove that very good success can be achieved with mechanical cleaning of the mucous membrane. In addition, a calomel therapy, lasting several days, should be used (b1); a single dose of calomel certainly was unsuccessful once (I, 13).

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On the whole, the result is that pure cultures of typhus bacilli are highly pathogenic for humans, even when they have been for a long time on synthetic culture media. Illness occurs just as easily as in feeding animals with highly virulent bacteria, in whom no infection usually begins, even with large amounts.

-END-